



PC10866AMGM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Weichao G. Chen, et al.

SERIAL NO.: 09/836,035

FILED: April 17, 2001

FOR: SODIUM-HYDROGEN EXCHANGER
TYPE 1 INHIBITORAssistant Commissioner For Patents
Washington, D.C. 20231

Examiner: E. Huang

Art Unit: 1625

I hereby certify that this correspondence
is being deposited with the United States
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Sir:

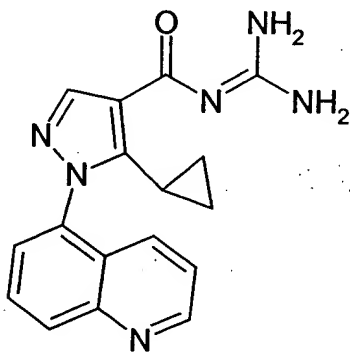
By

37 C.F.R. § 1.132 DECLARATION

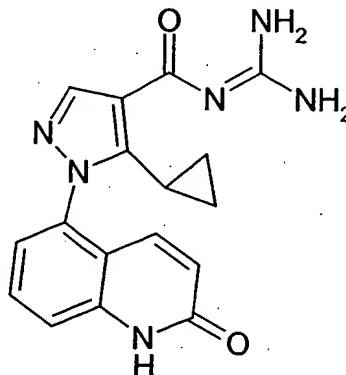
I, Mary C. Allen, a citizen of the United States residing at East Lyme, CT, hereby declare
as follows:

1. I obtained a Bachelor of Science degree in Biology in 1986 from Trinity College. In 1995, I earned a Masters of Science degree in Nutritional Biochemistry from the University of Connecticut. From 1986 to present, I have worked at Pfizer Inc where my current position is Senior Scientist.

2. I am familiar with the subject patent application entitled "Sodium-Hydrogen Exchanger Type 1 Inhibitor," filed April 17, 2001 (hereinafter "the instant application"). In particular, I am the pharmacokineticist who conducted plasma half-life analysis on the prior art Hamanaka compound (hereinafter "Compound A") and the instant application Formula I compound (hereinafter "Compound B").



COMPOUND A



COMPOUND B

3. I am familiar with the Office Action, dated July 16, 2001, issued in the instant application. In the Office Action, the Examiner contends that, absent unexpected results, one of ordinary skill in the art would be motivated to arrive at the invention in the instant application from disclosures in the prior art by Hamanaka (WO 99/43663). I am also generally familiar with Hamanaka (WO 99/43663).

4. The utility of Compound B versus Compound A, can be demonstrated by plasma half-life ($t_{1/2}$) measurements. The half-life is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

5. To measure plasma half-life, Compound A was administered as a 24 hour constant intravenous infusion dose to sixteen normal human subjects. Compound B is generated through metabolism via the aldehyde oxidase enzyme. Compound B is measured *in vivo* using an LC/MS/MS bio-analytical assay. A summary of the data is set forth below in Tables 1 and 2.

Table 1. Summary of Mean (SD) Pharmacokinetic Parameters of Compound A Following 24-h Continuous i.v. Infusion of Compound A

Dose (mg/kg/day)	T _{max} (h)	C _{avg} * (µg/mL)	AUC _{0-t} * (µg·h/mL)	AUC _{0-∞} * (µg·h/mL)	Cl _p (ml/min/kg)	V _{dss} (L/kg)	t _{1/2} (h)	% of Dose Excreted in Urine	Cl _r † (ml/min/kg)
1	5.4 (5.6)	0.04 (0.01)	1.05 (0.20)	1.05 (0.20)	16.0 (2.4)	0.9 (0.4)	2.7 (0.9)	21 (3.9)	3.3 (0.9)
3	4.4 (4.2)	0.11 (0.02)	2.86 (0.67)	2.87 (0.67)	17.7 (3.6)	1.3 (0.7)	3.1 (0.7)	22 (2.2)	4.0 (1.1)
10	9.0 (3.8)	0.44 (0.08)	11.6 (2.39)	11.6 (2.40)	14.6 (3.0)	0.6 (0.3)	5.0 (1.8)	20 (4.2)	2.9 (0.6)
20	16 (9.8)	1.10 (0.14)	27.7 (2.8)	27.7 (2.8)	12.1 (1.8)	1.0 (0.5)	5.7 (0.4)	18 (2.1)	2.2 (0.3)

t = the time of the last quantifiable plasma concentration; Values represent the mean ± SD of 4 subjects/dose.

* means and SD are geometric, all other means and SD are arithmetic.

† Renal clearance of unchanged drug.

Table 2. Summary of Mean (SD) Pharmacokinetic Parameters of Compound B Following 24-h Continuous i.v. Infusion of Compound A

Dose (mg/kg/day)	T _{max} * (h)	C _{max} † (µg/mL)	AUC _{0-t} † (µg·h/mL)	AUC _{0-∞} † (µg·h/mL)	t _{1/2} * (h)
1	24 (0)	0.11 (0.037)	2.31 (0.60)	2.40 (0.67)	7.7 (1.7)
3	24.0 (0.04)	0.25 (0.013)	5.90 (0.43)	6.06 (0.45)	7.1 (0.7)
10	24.13 (0.09)	0.74 (0.15)	17.6 (3.27)	18.0 (3.4)	6.8 (0.8)
20	24.04 (0.05)	1.18 (0.14)	30.3 (3.84)	30.9 (3.89)	6.8 (0.4)

t = the time of the last quantifiable plasma concentration; Values represent the mean ± SD of 4 subjects/dose.

* arithmetic means and SD

† geometric means and SD

6. Over the dose range tested, 1-20 mg/kg/day, the mean plasma half-life ("t_{1/2}") for Compound A was approximately 4 hours compared to t_{1/2} of 7 hours for Compound B. The fact that Compound B has a 3 hour longer t_{1/2} compared to Compound A is important because it may allow for more flexible dosing regimens and provide a longer duration of action, both of which are desirable attributes of this therapeutic agent.

7. Based upon my experience, a person of ordinary skill in the art would not have been able to predict that Compound B would have an almost two-fold improvement in half-life.

8. All statements made herein of my own knowledge are true and all statements made herein on information and belief are believed to be true; and further that these statements are made with the understanding that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATED: 11/16/01

Mary C Allen
Mary C. Allen



**BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE
UNITED STATE PATENT AND TRADEMARK OFFICE**

LIMITED RECOGNITION UNDER 37 CFR § 10.9(b)

Maria C. Laccotripe is hereby given limited recognition under 37 CFR §10.9(b) as an employee of Lahive & Cockfield, LLP, to prepare and prosecute patent applications where the patent applicant is the client of Lahive & Cockfield, LLP, and the attorney or agent of record in the applications is a registered practitioner who is a member of the Lahive & Cockfield, LLP. This limited recognition shall expire on the date appearing below, or when whichever of the following events first occurs prior to the date appearing below: (i) Maria C. Laccotripe ceases to lawfully reside in the United States, (ii) Maria C. Laccotripe's employment with Lahive & Cockfield, LLP ceases or is terminated, or (iii) Maria C. Laccotripe ceases to remain or reside in the United States on an H-1 visa.

This document constitutes proof of such recognition. The original of this document is on file in the Office of Enrollment and Discipline of the U.S. Patent and Trademark Office.

Expires: September 4, 2002.

A handwritten signature in black ink, appearing to read "Harry I. Moatz", written over a horizontal line.

Harry I. Moatz

Director of Enrollment and Discipline